Chemosaturation with percutaneous hepatic perfusion (PHP) Initial experience in Spain

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INTRODUCTION AND OBJECTIVES

The liver has been the primary target of the methods of regional chemotherapy with the aim of limiting toxicity of systemic chemotherapy. These methods allow high drug concentrations in tumors compared to systemic administration (Table 1).

The liver anatomical and functional nature allows to isolate the vascularization, high doses direct arterial chemotherapy administration, filter it in venous outflow and resist the toxic insult. Chemosaturation with percutaneous hepatic perfusion (PHP; Hepatic CHEMOSAT® Delivery System; Delcath Systems Inc, USA) is a regional therapy, repeatable and minimally invasive for unresectable hepatic metastases[1-6]. We describe the tolerance and results of the first two patients treated in Spain with chemosaturation with PHP.

Multiple Myeloma (label)	0.25 mg/kg
Chemoembolization	0.62 mg/kg
Surgical Isolated Hepatic Perfusion (IHP)	1.5 mg/kg
Percutaneous Hepatic Perfusion (PHP™)	3.0 mg/kg
Myeloablation	2.5-3.5 mg/kg

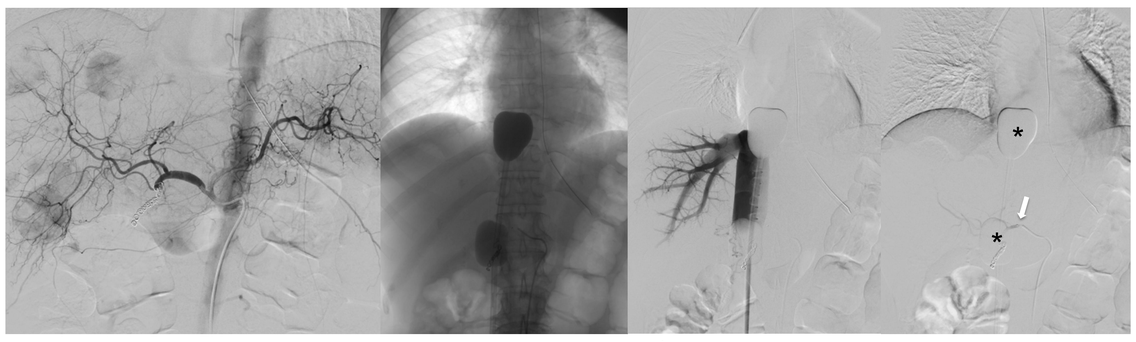
Table 1. Comparison of the melphalan dose to different treatments. PHP 10x drug dosing higher than FDA approved via systemic dose, and 100x drug dosing delivered to tumor that of systemic chemotherapy.

PATIENTS AND METODS

Two patients, a man and a woman 63 and 65 years old respectively, presented multiple liver metastases from uveal melanoma. The first patient had disease progression despite receiving systemic chemotherapy DTIC, and was scheduled for two sessions of chemosaturation-PHP with melphalan. The 2nd patient with liver and osseous metastases was treated with one session.

Prior to treatment, laboratory tests and full maging with computed tomography (CT) of the torax, upper abdominal magnetic resonance imaging (MRI) or computed tomography, and brain MRI were performed. Two weeks before PHP a complete liver visceral angiogram was performed and any branch with extrahepatic destination and origin in hepatic arteries was occluded. Tree days before allopurinol 300 mg/day was given, and the day before hydration 100-150 ml/h was started.

Treatment was planned by a multidisciplinary team comprised of oncologist, interventional and diagnostic radiologists, anesthesiologist, perfusionist, ICU, analyst, pharmacist, nursing and tech. The procedures were performed under general anesthesia-blood pressure control, and full anticoagulation ACT > 400 s in an interventional radiology suite. The vascular catheters were introduced percutaneously. A hepatic artery angiography was performed (Fig 1a) to verify that the previously embolized extrahepatic branches (Fig 1b) remained occluded. The catheter was positioned so that the agent was infused only into the liver. Perfusion of the agent into any other abdominal organ or gastrointestinal branches must be avoided as this may result in serious injury or death. Once the cava vein occlusion balloons were inflated (Fig 1c,d)), melphalan 3mg/kg, diluted in 500 ml saline, was given (Fig 1e) via pump in 30 min followed by 30 min washout. Hepatic venous effluent blood was filtered via extracorporeal hemofiltration as shown in Figure 2. Once the infusión finised, anticoagulation was reversed with protamine, catheters were removed and the patient was sent to the intensive care unit (ICU) for monitoring.



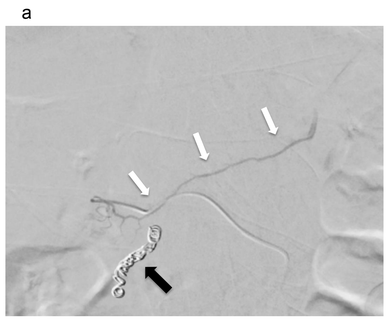


Fig.1 a, hepatic arteriography to verify that the previously embolized extrahepatic branches arising from hepatic arteries remained occluded; b, gastrointestinal artery ocluded with coils (black arrow) and the right gastric artery been occluded (withe arrows) in the procedure done two weeks before; c, double-balloon catheter percutaneously into the inferior vena cava to isolate (d) the hepatic venous blood; e, hepatic perfusión (white arrow) with melphalan during isolation of hepatic output with balloons (asterisks).

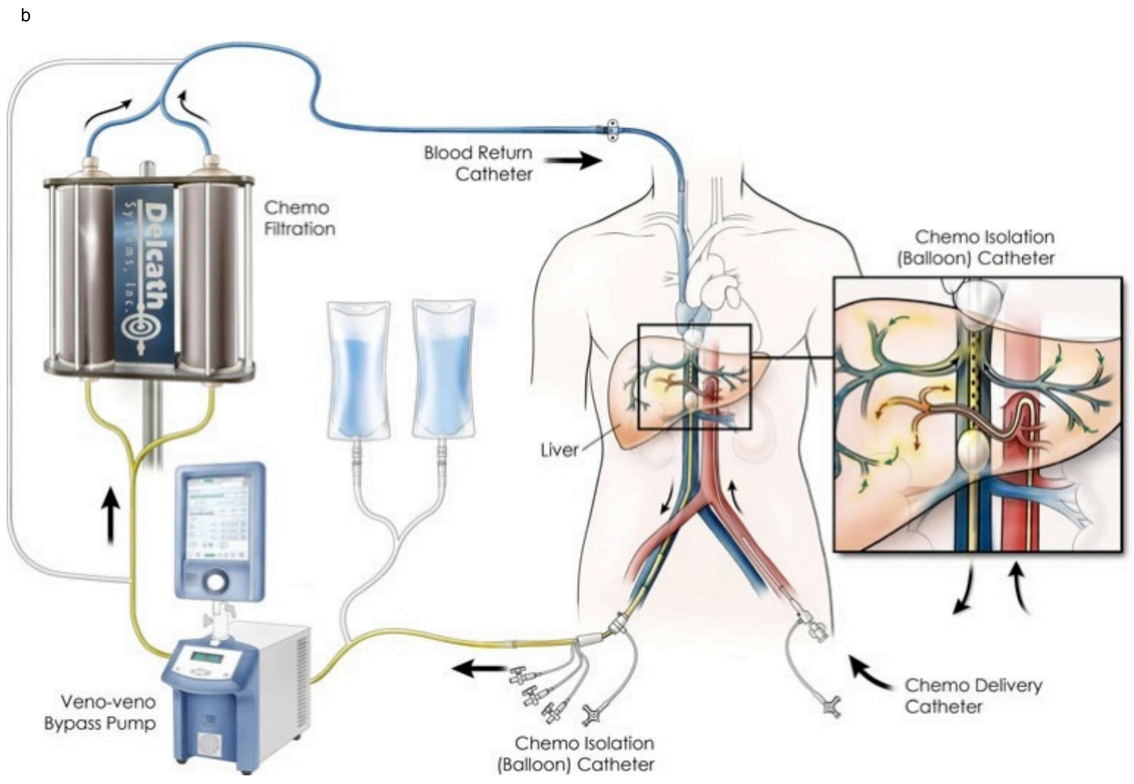


Fig.2 Chemosaturation-PHP drawing system (Hepatic CHEMOSAT Delivery System; Delcath Systems Inc., New York, NY) wich consists of a closed circuit of catheters and filters designed to deliver chemotherapy to the hepatic artery and then filter effluent hepatic venous blood before it is returned to the systemic circulation.

RESULTS

Operation room time was 4-5 hours. Deep bood pressure changes, during balloons inflation, needed high skills in anesthesia for mayor vascular procedures. After the procedure, patients remained in the ICU 24 hours. As described in literature, mild to moderate thrombocitopenia and anemia resulting from removal of platelets and red blood cells by the hemofiltration system, was observed immediately after the procedure.
Two of the three procedures required platelet, red blood cells and plasma transfusion. In all three procedures Ca^{++} decrease was observed and corrected in two. In the first 12 hours patients had polyuria in all procedures. No transient increases in liver transaminases were observed during the post-procedural period.
The hospital stay was 4-6 days.

Treatment response was measured with the changes in the sum of the diameters of all hepatic lesions. The first patient, wich received two sessions of chemosaturation-PHP, presented at 6 weeks a 44.6% tumor shrinkage (Fig 3a,b), and 72.3% at 6 months (Fig 3c,d). At the time of writing, one year after the first session, is still in progression-free survival (PFS). The second patient presented at 5 weeks a 55% tumor shrinkage (Fig 4) and is following. Table 2.

Response to treatment					
Patient 1 (Fig.2)	MR	First PHP Day 0	MR Day 44	2th PHP Day 127	MR Day 177
	184mm		102mm		51mm
		→ 44.6%		→ 50%	
		→ 72.3%			
Patient 2 (Fig.3)	CT	First PHP Day 0	CT Day 36		
	377mm		169mm		
		→ 55%			
Each new PHP-session reduced tumor by 50 %					

Table 2. Response to treatment. mm: sum of diameters whole liver mets.

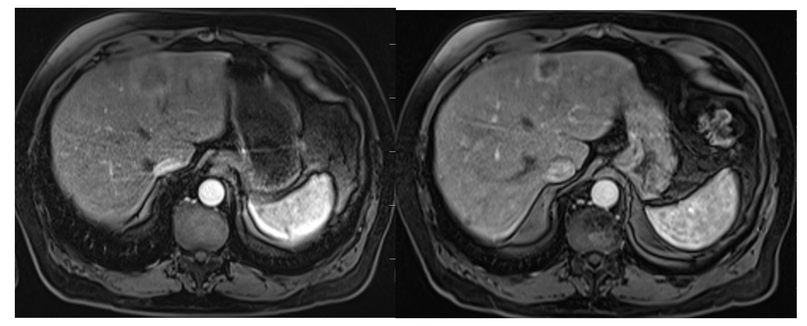


Fig.3 Magnetic resonance images (T1) of the first patient with diffuse liver metastases from uveal melanoma;
a. before treatment; b. 6 weeks after the first chemosaturation-PHP; c. 4 months after the first chemosaturation-PHP;
d. 7 weeks after the second chemosaturation-PHP and 6 months after the first chemosaturation-PHP.

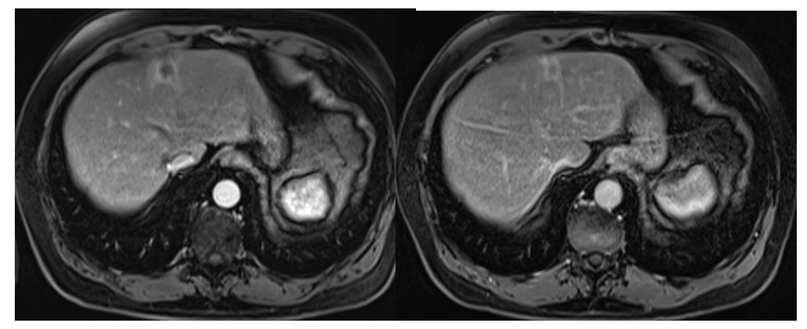
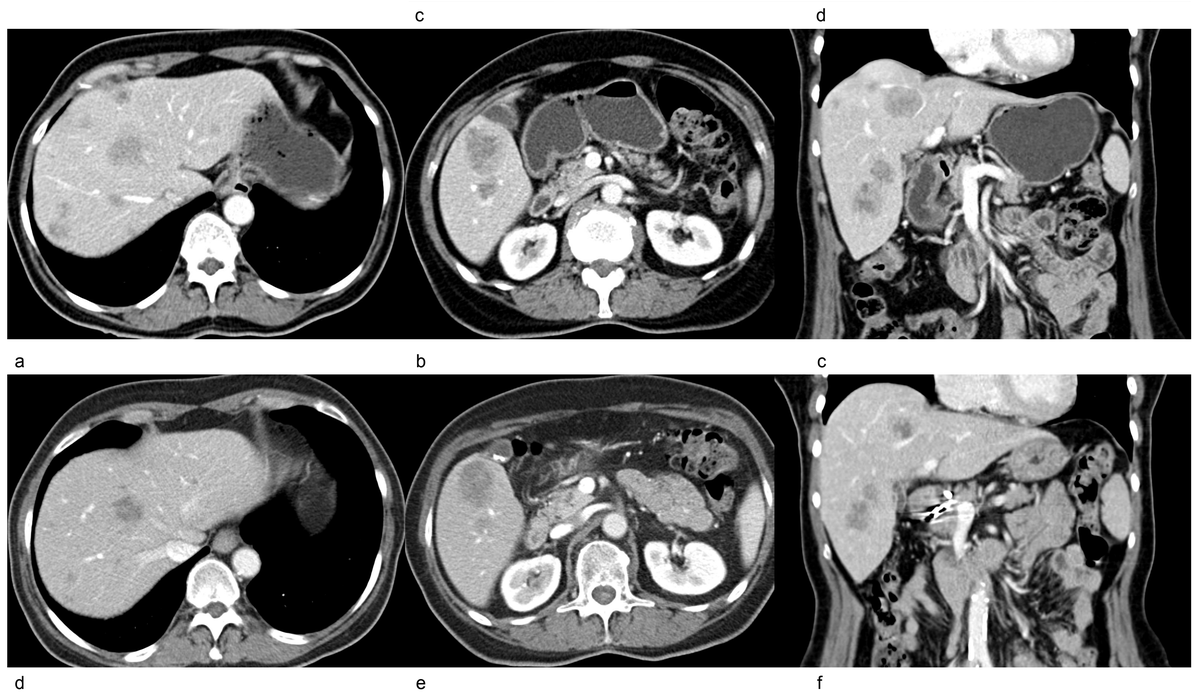


Fig.4 Computed tomography of the second patient with diffuse liver metastases from uveal melanoma;
a,b,c, before treatment; d,e,f, 5 weeks after the chemosaturation-PHP. Reduction of metastases volume and decrease in contrast enhancement is observed.



CONCLUSION

Chemosaturation with PHP is a minimally invasive whole organ new promising regional hepatic therapy. Technically not difficult but requires a very good team organization. Is repeatable. Despite high doses of melphalan tolerance is excellent.

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